REMARKS

Amendments to the Claims

Claims 27-30 have been canceled.

Claims 15, 32 and 33 have been amended to refer to a volume of between more than 0.5 mL and about 3.0 mL. Support is found in the specification, for example, at page 13, lines 7-10.

Claims 16, 17, and 20-23 have been amended to have correct dependency.

New Claim 34 has been added to recite wherein the cells are provided intra-operatively to a patient following harvest from the patient. Support is found in the specification, for example, at page 6, lines 8-11.

No new matter has been added. Entry of the amendments into the application is respectfully requested.

Priority

The Applicants maintain their arguments regarding priority as stated in the Amendment filed December 7, 2006 and June 12, 2007. On page 21, line 28 to page 22, line 9, the '948 application discloses administering autologous mesenchymal stem cells in accordance with the claimed invention.

The Office Action states that the '948 application does contain prophetic teachings of treatment with mesenchymal stem cells. Prophetic examples can be used to provide enabling support to claims. Reports of actual data are not required. *See Manual of Patent Examining Procedure (MPEP)* Section 2164.02, which states that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." Section 2164.01 of the MPEP states that the standard of enablement, *i.e.*, whether exprerimentation is undue or unreasonable, and the factors for that determination, is derived from *In re Wands*, and that "that standard is still the one to be applied." As discussed in detail in the previous Amendment, the claims were enabled by the disclosure in the '948 application, and are entitled to its filing date.

Rejection of Claims 1-3, 5-6, 10-16, 20-24, 31 and 33 Under 35 U.S.C. §103(a)

The Examiner has rejected Claims 1-3, 5-6, 10-16, 20-24, 31 and 33 under 35 U.S.C. § 103(a) as being unpatentable over Sakai *et al.*, "Transplantation of Mesenchymal Stem Cells Embedded in Atelocollagen® Gel to the Intervertebral Disc: A Potential Therapeutic Model for Disc Degeneration," *Biomaterials, 24*: 3531-3541 (September 2003) ("Sakai").

The Examination Guidelines ("the Guidelines") for Determining Obviousness under 35 U.S.C. §103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register, Vol. 72, No. 195, page 57526-57535, state that "[a]s reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.* Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(1) Determining the scope and content of the prior art;

(2) Ascertaining the differences between the claimed invention and the prior art; and

(3) Resolving the level of ordinary skill in the pertinent art."

Applicants are the first to disclose treatment of degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. Claim 1 is directed to administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. As discussed above, Claims 15, 32 and 33 have been amended to recite administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation with a volume of between more than 0.5 mL and about 3.0 mL.

Sakai does not teach or suggest Applicants' claimed invention, particularly as amended. Sakai discloses use of cultured mesenchymal stem cells for the treatment of intervertebral disc degeneration, using a rabbit model. The cultured cells were embedded in Atelocollagen® and 0.04 ml of the solution was transplanted in discs of rabbits. One of ordinary skill in the art would not be motivated to practice Applicants' claimed invention of using uncultured mesenchymal stem cells in the claimed volume with a reasonable expectation of success.

The Examiner states that: "Sakai [ ] practices a more difficult method in culturing mesenchymal cells solely in order to label them (ie, applicant has not disclosed an easier or more

efficient way, it is just that Sakai et al must demonstrate that the therapeutic cells survived and the method worked) and expand them." (page 5) Applicants respectfully disagree. Sakai has failed to show that the cells disclosed therein were clinically therapeutic and Sakai did not show that the Applicants' methods worked.

Applicants maintain their arguments from the Amendment filed December 7, 2006 and June 12, 2007 and further state that, at the time of the invention, culturing was generally used not only to mark cells, but also to expand and differentiate cells. It was standard practice in the art to culture clinically useful cells. The references discussed in the previous amendment were published at or before the time of the invention and all teach culturing clinically useful cells outside of the context of marking, and demonstrate that one of ordinary skill in the art at the time of the invention would have been motivated to culture cells prior to administration. As previously noted, these references all require culturing of cells prior to implantation. These references demonstrate that one of ordinary skill in the art at the time of the invention would have been motivated to culture cells prior to implantation, in order to expand and differentiate cells.

The Examiner also states that Applicants' arguments that the method of Sakai cannot be used as a therapeutic are not persuasive because Sakai demonstrates the effectiveness of the treatment. The Examiner's conclusion that Sakai's method is therapeutically useful is based on impermissible hindsight using Applicants' specification. Sakai's teachings merely demonstrate proof of the concept that autologous cultured mesenchymal stem cells delivered to a degenerating disc resulted in preservation of disc structure and differentiation of cells providing "new hopes" for treatment of degenerative disc disease in humans. Sakai concludes that "our study provide *initial* evidence for the *potential* of MSCs to differentiate into [invertebral] cells, which provides new information in MSC research." (Sakai page 3539, second column, emphasis added). In the abstract from the *Annual Meeting of the International Society for the Study of the Lumbar Spine*, dated May 2003 ("Abstract"), the Sakai et al. state "[o]ur study has implicated the *potential* of MSCs to differentiate into intervertebral disc cells, which provides new information in MSC research." (emphasis added).

In fact, there are a number of reasons why Sakai's method would not be therapeutically useful in applicants' claimed methods:

First, Sakai's method would result in magnifying contamination of the cell population. Culturing stem cells may result in magnifying contamination from other cells, such as fibroblast cells, which grow ten times faster than stem cells. Thus, culturing stem cells does not result in a pure stem cell population.

Second, Sakai's method cannot be used for therapeutic use or formulation. Culturing stem cells involves expanding the cell population by adding a wide range of solutions, such as Dulbecco's modified eagle media (DMEM). DMEM contains phenol which is a hazardous chemical to the human body. Sakai does not disclose how to overcome the DMEM toxicity. In contrast, such materials would not normally be present in a formulation containing uncultured cells.

Third, Sakai's culturing of stem cells would not be desirable for treatment of degenerative disc disease because culturing results in a large stem cell population. It is not desirable to have a large stem cell population because one would not want to overburden the bodily system with nutritional requirements for feeding large numbers of such cells. In addition, the degenerative disc can only hold a limited number of cells.

Fourth, one of the most serious disadvantages from using uncultured cells is that, because the culturing takes weeks to perform, there is an increased risk that the patient will receive some other person's cells by mistake. This disadvantage is particularly addressed by the intraoperative aspect of the invention.

Objective evidence of nonobviousness

In addition, the Guidelines state that secondary considerations, such as commercial success, long-felt but unresolved needs, failure of others, and unexpected results must be evaluated.

The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would *not* have been obvious to those skilled in the art when it was invented.

On pages 5-6, the Office Action states that "Applicants have not performed the method of Sakai et al without expending the cells by culture. Yet, one skilled in the art, having read Sakai et al, *would know that the method would work* without culturing the cells." (emphasis added)

Further, on page 5, the Office Action states that "[w]hile expansion gives more cells, immediate transplantation offers the *obvious advantage* of immediate delivery and treatment." (emphasis added).

However, the claimed invention has satisfied a long-felt need in the relevant field. The contemporaneous references discussed above require culturing of cells, which, in turn, necessitates a delay in treating the patient's degenerating disc. Applicants' claimed method of administering uncultured mesenchymal stem cells, particularly in a formulation in the volume recited in the amended claims, is advantageous for a number of reasons, including the fact that, because the process permits the patient to undergo the procedure of removal of cells from the bone marrow while the patient is already under general anesthesia to undergo the surgery required to administer the cells to the degenerative disc. Nonetheless, Applicants' methods had not been performed prior to Applicants' application.

Sakai does not teach or suggest that administration of uncultured autologous MSCs, particularly in the formulation in the volume recited in the amended claims, would be therapeutically useful in Applicants' claimed invention.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6, 10-16, 20-24, 31 and 33 Under 35 U.S.C. §103(a)

The Examiner has rejected Claims 1-6, 10-16, 20-24, 31 and 33 under 35 U.S.C. § 103(a) as being unpatentable over Sakai in view of Tanny, G.B. *et al.*, "Improved Filtration Technique for Concentrating and Harvesting Bacteria," *Appl. Environ. Microbiol., 40*(2):269-273 (1980).

As discussed above, Claims 15, 32 and 33 have been amended to recite administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited.

According to the Examiner on page 6, Applicants' arguments that using uncultured cells is novel and non-obvious is not found persuasive because Applicants have "simply skipped a step that was required for Sakai et al to demonstrate therapeutic value but is not required, precisely because Sakai et al demonstrated it, in the instant method." However, as described above, Sakai does not teach that his method is therapeutically useful.

Applicants maintain their arguments from the Amendment filed December 7, 2006 and June 12, 2007 and state that, as indicated above, Sakai does not teach Applicants' therapeutic

method for delivering uncultured mesenchymal stem cells, particularly in a formulation in the volume recited. Tanny teaches concentrating cells by filtration and harvesting bacterial cultures. As discussed in Tanny, the bacterial cells were cultured. In addition, Tanny does not teach or suggest administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited.

The Examiner's combination of these two references, which teach culturing of cells, reinforces Applicants' argument that culturing was standard practice at the time of the invention. None of the references alone or teach in combination teach or suggest treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited. One of ordinary skill in the art would not be motivated to combine the teachings of Sakai with Tanny, based on these references or the knowledge of one of ordinary skill in the art, with any reasonable expectation of success in treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited. Therefore, the invention is not obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5-7, 10-16, 18, 20-24 and 31-33 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-7, 10-16, 18, 20-24 and 31-33 under 35 U.S.C. § 103(a) as being unpatentable over Sakai in view of Russell *et al.* "Human Bone Marrow Mesenchymal Stromal Cells as a Source of Chondrocytes for Treatment of Intervertebral Disc Degeneration," 27, Abstracts of the 30th Annual Meeting of the International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003).

As discussed above, Claims 15, 32 and 33 have been amended to recite administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited.

According to the Examiner on page 7, Applicants' arguments are not found persuasive for the reasons indicated. Applicants maintain their arguments from the Amendment filed December 7, 2006 and June 12, 2007 and further state that, as indicated above, Sakai does *not*

teach a therapeutic method for delivering uncultured mesenchymal stem cells in a formulation in the volume recited.

Russell teaches the use of human bone marrow mesenchymal stromal cells as a source of chondrocytes for the treatment of intervertebral disc degeneration. In addition, Russell teaches that the mesenchymal stem cells were cultured in the presence of TGF-β1. Further, Russell, does not teach or suggest administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited.

The Examiner's combination of these two references, which teach culturing of cells, reinforces Applicants' argument that culturing was standard practice at the time of the invention. One of ordinary skill in the art would not be motivated to combine the teachings of Sakai with Russell, based on these references or the knowledge of one of ordinary skill in the art, with any reasonable expectation of success in treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited. Therefore, the invention is not obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5-7, 10-17, 18, 20-24 and 31-33 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-7, 10-17, 18, 20-24 and 31-33 under 35 U.S.C. § 103(a) as being unpatentable over Sakai in view of Russell *et al.* "Human Bone Marrow Mesenchymal Stromal Cells as a Source of Chondrocytes for Treatment of Intervertebral Disc Degeneration," 27, Abstracts of the 30th Annual Meeting of the International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003).

As discussed above, Claims 15, 32 and 33 have been amended to recite administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the specified volume. According to the Examiner on page 7, Applicants arguments are not found persuasive for the reasons indicated. Applicants maintain their arguments from the Amendment filed December 7, 2006 and June 12, 2007 and further state that, as indicated above, Sakai does not teach a therapeutic method for delivering uncultured mesenchymal stem cells in a formulation in the volume recited. Russell teaches the use of

human bone marrow mesenchymal stromal cells as a source of chondrocytes for the treatment of intervertebral disc degeneration. In addition, Russell teaches that the mesenchymal stem cells were cultured in the presence of TGF-β1. Further, Russell does not teach or suggest administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited.

The Examiner's combination of these two references, which teach culturing of cells, reinforces Applicants' argument that culturing was standard practice at the time of the invention. None of the references alone or teach in combination teach or suggest treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited. One of ordinary skill in the art would not be motivated to combine the teachings of Sakai with Russell, based on these references or the knowledge of one of ordinary skill in the art, with any reasonable expectation of success in treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc in a formulation in the volume recited. Therefore, the invention is not obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

In addition, Applicants respectfully request that the Examiner acknowledge and consider the references filed in the Information Disclosure Statements filed on September 15, 2006, October 13, 2006, February 26, 2007 and April 13, 2007.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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